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MYERS, C	
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DATE MAILED: 05/10/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 10/3/95 + 2/20/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892. 2 sheets
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449. 2 sheets
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☑ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-38 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-38 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

1. This action is in response to the amendment of Paper No. 9, filed 11/12/96. Applicants arguments have been fully considered but are not persuasive to overcome all current grounds of rejection. This action is made final.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicants must comply with the requirements of 37 CFR 1.821-1.825 in response to this Office action. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing the disclosed sequences (see, for example, page 21), an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

In the response of Paper No. 9, Applicants state that a separate statement regarding the sequence listing is being filed. However, it is pointed out that the Office has not received the paper copy or CRF of the Sequence Listing. An amendment directing the entry of a paper copy of the Sequence listing and a letter stating that the content of the paper and computer readable copies are the same are required.

4. The rejection of claim 36 under 35 U.S.C. § 101 and the rejection of claims 6, 13-23, 26, 37 and 38 under 35 U.S.C. § 112, second paragraph, are withdrawn in view of the amendment to the claims.

5. Claims 1-30 and 32-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,429,923. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '923 are inclusive of methods for diagnosing hypertrophic cardiomyopathy wherein the method comprises detecting the presence or absence of a hypertrophic cardiomyopathy associated mutation in the RNA of an individual. It is noted that the claims of '923 do not recite packaging the reagent required to perform the diagnostic method in a kit. However, reagent kits for performing DNA diagnostic assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the primers and probes required for the detection of hypertrophic cardiomyopathy associated-mutations in a kit for the expected benefits of convenience and cost-effectiveness.

In the response of Paper No. 9, Applicants state that a terminal disclaimer will be filed upon indication of allowable subject matter if appropriate. Accordingly, the rejection is maintained for the reasons of record.

6. The rejection of claims 1-31 and 36-38 under 35 U.S.C. § 102(a) as being anticipated by Rosenzweig et al, the rejection of claims 1-31 and 36-38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Watkins et al, and the rejection of claims 33-35 under 35 U.S.C. § 103 as being unpatentable over Rosenzweig or Watkins in view of the Stratagene Catalog are withdrawn in view of the 132 declaration filed 11/12/96.

7. Claim 36 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Eisenberg.

Eisenberg teaches RNA probes complementary to the sequences of the *B*-MHC nucleic acids (see page 289). The probes are considered to have the property of being useful for facilitating diagnosis of hypertrophic cardiomyopathy because the probes of Eisenberg hybridize to and thereby are capable of detecting changes in the *B*-cardiac myosin heavy chain DNA. Accordingly, Eisenberg anticipates the invention of claim 36.

Applicants traversed this rejection by stating that Eisenberg does not teach or suggest a probe useful for facilitating diagnosis of hypertrophic cardiomyopathy. However, it is a property of the probe disclosed by Eisenberg that it would be useful for diagnosing hypertrophic cadiomyopathy because the probe is capable of hybridizing to and detecting *B*-cardiac myosin heavy chain DNA.

8. Claims 37 and 38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Friedman.

Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 109). Accordingly, Friedman anticipates the invention of claims 37 and 38.

Applicants traverse this rejection by stating that Friedman does not teach primers useful for the detection of hypertrophic cadiomyopathy and assert that Friedman teaches away from the claimed invention because the reference teaches that mutations could not be identified in exon 13 of patients with MHC. These arguments are not persuasive because it is a property of the primers taught by Friedman that they are useful in the

diagnosis of hypertrophic cadiomyopathy because the primers are capable of amplifying the *B*-MHC DNA and thereby could be used for diagnostic analysis of the sequences of the amplified *B*-MHC DNA.

9. Claims 37 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman.

Feldman teaches compositions comprising sets of PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 1867). The compositions of Feldman contain 13 pmol of each primer and therefore are considered to comprise at least 4 oligonucleotides. Accordingly, Feldman anticipates the invention of claims 37 and 38.

In the response of Paper No. 9, Applicants traverse this rejection by stating that Feldman teaches gene expression of *B*-MHC by PCR, but does not teach primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy. However, it is a characteristic of the primers taught by Feldman that they are useful in the diagnosis of hypertrophic cadiomyopathy because the primers are capable of amplifying the *B*-MHC DNA and thereby could be used for diagnostic analysis of the sequences of the amplified *B*-MHC DNA.

10. The rejection of claims 24-30 under 35 U.S.C. § 102(b) as being anticipated by Almoguera, and the rejection of claim 31 under 35 U.S.C. § 103 as being unpatentable over Almoguera in view of Mullis are withdrawn in view of the amendment to limit the claims to methods for identifying a hypertrophic cardiomyopathy-associated mutation.

11. Claims 33-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera and further in view of the Stratagene Catalog.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labelled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic myocardiopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labelled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic myocardiopathy associated mutations in *B*-MHC nucleic acids.

Modification of the method of Geisterfer-Lowrance as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the B-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits

provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claim 35, it would have been further prima facia obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents. It is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)).

Applicants traverse this rejection by stating that Geisterfer-Lowrance only demonstrates that afflicted members of a single family with FHC have the mutation and that in the absence of extensive studies on the correlation between the mutation and HC, there would not have been a reasonable expectation of success of the claimed methods or a suggestion for a collection of reagents in a kit.

Applicants arguments have been fully considered but are not persuasive. It is pointed out that in claims to products, such as kits, the intended use of the product carries no weight. While the teachings of Geisterfer-Lowrance may not have been sufficient to enable absolute diagnosis of HC, the prior art suggests use of the disclosed sequences to amplify *B*-MHC nucleic acids and to identify mutations. Accordingly, the prior art when considered as a whole

would have suggested the claimed kits for the benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify and identify mutations in the *B*-MHC nucleic acids.

THE FOLLOWING NEW GROUNDS OF REJECTION WERE NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

12. Claims 36 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is indefinite over the recitation of "by being arranged for use" because it is unclear as to what is intended to be meant by a probe being arranged for use in a detection method.

Claim 39 is indefinite over the recitation of "said primers comprising at least two oligonucleotides" because it is not clear as to whether the claim is intended to be limited to primers which are made up of at least two of the recited oligonucleotides or if the claims are intended to be limited to sets of primers wherein the set comprises at least two of the recited oligonucleotides. In the former case, it is not clear as to whether the oligonucleotides are linked or in some other way connected.

13. Claims 24-26, 28-30 and 43 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Mullis.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations

associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. The reference (see abstract) states that the "(i)dentification of two unique mutations within cardiac MHC genes in all individuals with FHC from two unrelated families demonstrates that defects in the cardiac MHC genes can cause this disease". Geisterfer-Lowrance does not teach amplifying the sample *B*-MHC nucleic acid prior to determining the sequence of the DNA.

Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis also teaches amplifying nucleic acids by PCR prior to sequencing (see column 36). The reference states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have amplified the B-MHC nucleic acids prior to sequence analysis in order to have increased the quantity of the target DNA and thereby to have increased the overall sensitivity of the detection of

hypertrophic cardiomyopathy associated point mutations in the *B*-MHC nucleic acids.

14. Claim 27 is rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labelled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with disea-

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic myocardiopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labelled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic myocardiopathy associated mutations in *B*-MHC nucleic acids.

Applicants arguments directed to the previous grounds of rejection are addressed below as they apply to the instant grounds of rejection. Applicants traverse this rejection by stating that Geisterfer-Lowrance only demonstrates that afflicted members of a single family with FHC have the mutation and that in the absence of extensive studies on the correlation between the mutation and HC, there would not have been a reasonable expectation of success of the claimed methods. These arguments are not persuasive because the claims are not directed to methods of diagnosis but rather only to methods for identifying mutations in the *B*-MHC gene. Geisterfer-Lowrance provides the motivation and reasonable expectation for identifying these mutations in other nucleic acid samples because the reference provides the methodology for detecting such mutations and it would have been well within the skill of the art to have practiced these conventional methods to effectively accomplish the analysis of nucleic acids for mutations. Furthermore, the reference provides the motivation to analyze additional samples for the stated mutations because the reference teaches that further assays should be performed to determine if

the mutation is present in other families and states that use of genetic probes to MHC mutations will be important in facilitating our understanding of the function of MHC and the causes of HC. Accordingly, the cited prior art suggests and provides a high expectation of success of employing methods for the detection of mutations in MHC.

15. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e) were filed prior to or with the payment of the fee set

forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for this Group is (703)-305-7401.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 26, 1997

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER
GROUP 1800